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APPLICATION No.	FILE No./Date	CLASS. NAME/CLASS No.	EXAMINER	STATUS
09/234,182	01/29/1996	7,415,881 HSE		

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EXAMINER

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DATE MAILED 4/12/96

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Please find below and or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/234,182

Applicant(s)

HSEI ET AL.

Examiner

Jessica H. Roark

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 October 2002 and 22 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 19-22, 26-29 and 31-36 is/are pending in the application.
- 4a) Of the above claim(s) 2-4, 6, 7, 20, 22 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 5, 19, 21, 26, 28, 29 and 31-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 January 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Paper No. 31.

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RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/21/02 (Paper No. 24), is acknowledged.
Claims 8-18, 23-25 and 30 have been cancelled previously.
Claims 1-7, 19-22, 26-29 and 31-36 are pending.

Claims 2-4, 6-7, 20, 22 and 27 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention, election having been confirmed without traverse in Paper No. 15.

Claims 1, 5, 19, 21, 26, 28-29 and 31-36 are under consideration in the instant application.

2. This Office Action will be in response to applicant's arguments, filed 10/21/02 (Paper No. 24).
The rejections of record can be found in the previous Office Action (Paper No. 23).

Drawings

3. Applicant's petition filed under 37 CFR 1.84(a)(2) has been denied. Please see Paper No. 31, attached hereto.
4. The drawings filed 1/22/03 have been approved by the Draftsman.

IDS

5. Applicant's re-provision of the references cited on the IDS filed 6/8/99 (Paper No. 4) and the IDS filed 10/26/99 (Paper No. 5) is gratefully acknowledged.

These references have now been considered as shown by initialing on the attached copy of form PTO-1449.

Specification

6. Applicant's correction of the ATCC address on page 207 at lines 8-9 is acknowledged. However, the ATCC address should also be corrected on page 240 in the paragraph beginning at line 7 (as amended on 10/21/02).

Applicant is reminded that the current address of the ATCC is:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Applicant is requested to review the specification to determine if the incorrect address occurs elsewhere.

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Claim Rejections - 35 USC § 112 first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 5, 19, 21, 26, 28-29 and 31-36 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments, filed 10/21/02, have been fully considered but have not been found convincing for the reasons of record.

Applicant argues that Example "T" of the specification provides methods for protection of a free cysteine with PDS and subsequent deprotection with DTT. Applicant asserts that in view of this disclosure it would not require undue experimentation for the skilled artisan to protect the carboxy terminal PEG of the Fab' fragment before coupling of a single PEG to the "interchain" cysteine.

The Examiner acknowledges that the skilled artisan can protect and deprotect cysteines. However, at issue is whether Applicant has provided sufficient guidance as to how one free cysteine can be protected while another is not.

Although several conjugates of antibodies and antibody fragments to PEG are disclosed in the specification (e.g., the conjugation of a single PEG to the free thiol of the unpaired cysteine at the COOH terminus of the Fab' fragment, as disclosed on pages 216-220 of the specification); the Examiner maintains that the instant claims require limitations in terms of number and placement of the covalent attachments that do not appear to be supported in the specification as filed by a sufficiently enabling disclosure.

As previously noted, the instant claims require that the recited Fab' fragment be covalently attached to a single PEG. The expression vector disclosed in the specification for use in producing an Fab' fragment is derived from human IgG1 and has a free cysteine at the carboxy terminus of the heavy chain (see page 216). As disclosed in the example on pages 216 to 220, it is this cysteine at the carboxy terminus of the Fab' fragment that was used in the working example of pages 216-220 of the specification to couple a single PEG molecule to the Fab' of interest. The human IgG1 Fab' structure permits coupling of a single PEG because only the cysteine at the carboxy terminus is available for the coupling reaction - the other cysteines present in the heavy and light chain components of the Fab' fragment are involved in either intrachain or interchain disulfide bridges (e.g., see the schematic representation of the five classes of human immunoglobulins in Figure 14 of Chapter 9 of "Fundamental Immunology", Second Edition, W.E. Paul editor, Raven Press Ltd., New York, 1989, page 225, of record).

The instant claim language requires that, although the single antibody Fab' fragment must be covalently attached to a single PEG, the Fab' fragment also is modified so that a cysteine ordinarily involved in the formation of the heavy-light chain interchain disulfide bridge is covalently coupled to the PEG. However, an Fab' fragment as recited has two reactive cysteines, rather than one, and the skilled artisan would not reasonably expect that such a modified Fab' fragment could be coupled to only a single PEG, as required in the instant claims.

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Thus the Examiner maintains that the specification does not appear to provide sufficient guidance as to how only a single PEG, as currently recited, may be covalent coupled to the recited Fab' fragment having two reactive cysteines. The specification does not disclose, and the state of the art at the time the invention was made did not recognize, methodology for protecting the free cysteine already present in the Fab' fragment so that PEG may be coupled only to an "interchain" cysteine.

Applicant has failed to provide sufficient objective evidence that it is possible to selectively protect one versus another of the *two free* cysteines present in the instantly recited mutated Fab' molecule.

Thus it would require undue experimentation of the skilled artisan to determine how to covalently couple a *single* PEG to an Fab' fragment in which one of the cysteines which ordinarily forms a disulfide bridge with another cysteine present in the opposite chain (i.e., using a cysteine ordinarily part of the heavy-light interchain disulfide bridge) is required by the claim language to be covalently coupled when insufficient guidance is provided as to avoid coupling of the second free cysteine present at the carboxy terminus of the Fab' fragment.

The rejection is therefore maintained.

35 U.S.C. § 102

9. The Declaration under 37 CFR 1.132 filed 10/21/02 is sufficient to overcome the rejection of claims 1, 5, 19, 21, 26, 28-29 and 31-36 based upon either U.S. Pat. No. 6,133,426 (of record) or U.S. Pat. No. 6,025,158 (of record) by establishing that the invention disclosed but not claimed in the '426 and '158 patents was not "by another".

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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11. Claims 1, 5, 19, 21, 31-35 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, 32-37 of copending Application No. USSN 09/489,394. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '394 application recite all the limitations recited in the instant claims, indicating that the limitations set forth in the instant claims were obvious embodiments of the invention claimed in USSN 09/489,394.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments, filed 10/21/02, have been fully considered but have not been found persuasive.

Applicant's comments regarding the different scope of the claims are acknowledged. However, the provisional rejection of record did not require that the claims be of the same scope, but rather, was set forth as an obviousness-type double patenting provisional rejection. In particular, it is noted that, contrary to Applicant's assertions, the claims of USSN 09/489,394, at least at the time the provisional obviousness-type double patenting rejection was made, did recite that the PEG was added to a cysteine ordinarily present in a disulfide bridge with a cysteine present in the opposite chain.

Co-pending application USSN 09/489,394 was not available to the Examiner for review during the preparation of this Office Action.

If Applicant's arguments relied upon an amendment to the claims of co-pending application USSN 09/489,394; Applicant is invited to provide a copy of the current co-pending claims to establish that the inventions currently claimed in the instant application and co-pending application USSN 09/489,394 are patentably distinct.

However, until such time as it is established that the claims are patentably distinct, the rejection is maintained.

12. Claims 1, 5, 19, 21, 31-35 are directed to an invention not patentably distinct from claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, 32-37 of commonly assigned USSN 09/489,394 for the reasons set forth supra.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned USSN 09/489,394, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. *Failure to comply with this requirement will result in a holding of abandonment of the application.*

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

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13. The provisional obviousness-type double patenting rejection of claims 1, 5, 19, 21, 26, 28-29 and 31-35 as being unpatentable over claims 1, 5, 8, 12-19, 21, 24-26 and 28-35 of copending Application No. USSN 09/726,258 is withdrawn.

Conclusion

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
March 31, 2003

PHILLIP GAMBEL, PH.D.
PRIMARY EXAMINER

RECEIVED CENTER 1600
3/31/03